



Original Communication

Pulmonary embolism and sudden-unexpected death: Prospective study on 2477 forensic autopsies performed at the Institute of Legal Medicine in Seville

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ABSTRACT

Pulmonary embolism (PE) and deep venous thrombosis (DVT) are clinical manifestations of the same entity, venous thromboembolic disease (VTD). In approximately 25% of patients, the first manifestation of PE is sudden-unexpected death.

We carried out a prospective study at the forensic pathology service of the Institute of Legal Medicine in Seville with the aim to know the incidence of PE as well as to describe the epidemiological, pathological and clinical characteristics of these deaths and associated risk factors.

In the study period (32 months) 32 cases of PE were registered from a total of 2447 completed autopsies. Three cases were considered accidental deaths and the remaining 29 cases were sudden natural deaths, which represents 1.3% of the total autopsies, 2.6% of natural deaths and 4.3% of sudden deaths. Nineteen cases (59%) were men (mean age 50.3 ± 13.8 , range 22–74 years) and 13 cases (41%) were women (mean age 50.3 ± 13.8 , range 18–87 years). In 78% of cases death occurred at home or during transfer to a health care centre, mainly during the fall or winter (69%) and between 8 a.m. and 4 p.m. (47%). Pulmonary infarction was associated only in two cases (6%). Nine cases (28%) had been immobilized but only three (9%) received anticoagulant therapy. Surgical interventions had occurred in seven cases (22%). A history of psychiatric pathology was found in 31%. Overweight or obesity was found in 75%. The most frequent symptoms prior to death were dyspnea (31%) and chest pain (19%), and 19% of patients were examined in an Emergencies Department for symptoms compatible with deep vein thrombosis and/or PE, but this diagnosis was not suspected in any case.

PE frequently makes its first appearance as sudden death. In addition to the classic risk factors, this study highlights that 75% of the cases were overweight/obese as well as 31% having had a history of psychiatric disorders and treatment as to support that this association should be considered as a risk factor. PE continues to be under diagnosed in Emergencies Department patients, which hinders the application of adequate therapeutic measures to prevent these deaths.

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1. Introduction

Pulmonary embolism (PE) and deep venous thrombosis (DVT) are clinical manifestations of the same entity, venous thromboembolic disease (VTD). The clinical diagnosis of PE is difficult in a significant percentage of patients and is frequently missed, explaining its high mortality rate.^{1,2} In approximately 25% of patients, the first manifestation of PE is sudden-unexpected death.^{3,4}

Thrombus formation is based in the classical Virchow's triad: Stasis, endothelial damage and abnormalities in the circulating blood. The predisposition to form clots may be due to acquired or genetic risk factors. Acquired risk factors include immobilization, increasing age, surgery, malignancies, obesity, pregnancy, puerperium, oral contraceptives and long-haul air travels.^{2,5} Inherited conditions (hereditary thrombophilias) include factor V Leiden leading to activated protein C resistance, prothrombin gene mutation, and deficiencies of antithrombin (I, II and III), protein C or protein S.^{6–10}

PE is a well-known entity in forensic pathology and is described in most standard Forensic Pathology textbooks^{11,12} as well as in some recent studies from medical examiners offices.^{7–10} There are also other studies on clinical autopsies on previously hospitalized

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patients.^{13,14} However, most previous series are retrospective; on the contrary, the main strength of our study is that it has been conducted prospectively, in a consecutive series of forensic autopsies.

The objective of this study is to analyze the incidence of PE as the cause of sudden death in the reference population of the forensic pathology service of the Institute of Legal Medicine, Seville, determining the absolute number of these deaths and their percentage in relation to the total number of deaths and specifically to the natural deaths. The epidemiological, pathological and clinical characteristics of these deaths are described as well as the presence of risk factors.

2. Material and methods

According to the Spanish Legislation, all cases of violent or suspected deaths must undergo a medico-legal investigation with the aim to know the cause and the manner of the death. These cases include: homicides, suicides or accidents of any kind, sudden-unexpected deaths, deaths in custody, deaths at home or in hospital when the cause is unknown and no death certificate is issued, and patients under the care of a physician, at home or in hospital, when the family present a complaint asking for a judicial inquire because a medical negligence is alleged.

We carried out a prospective study of all forensic autopsies performed at the forensic pathology service (Institute of Legal Medicine, Seville, with a reference population of 1,835,077 inhabitants) in a period of 32 months, from November 1st 2003 until June 30th 2006. All cases of deaths in which the pathological diagnoses was PE, either associated or not to DVT, were included in the study. The cases were classified as traumatic deaths or sudden natural deaths if they were or were not linked back to an initiating traumatic episode.

Sudden, unexpected death was defined, according to commonly accepted criteria, as a natural death that occurs within 6 h of the beginning of symptoms in an apparently healthy subject or one whose disease was not so severe that a fatal outcome would have been expected.¹⁵ Also those cases were included where death was not witnessed but the person was seen healthy or with a stable previous pathology in a period not greater than 24 h ante-mortem.

All the autopsies were performed with a post-mortem delay of less than 18 h according to the Recommendations on the Harmonization of Medico-Legal Autopsy Rules produced by the Committee of Ministers of the Council of Europe.¹⁶ Specifically, a protocol was followed which included: clinical histories of the case, height, weight, abdominal perimeter, complete macroscopic autopsy with weight of all organs, examination of the pulmonary arterial trunk by posterior approach to diagnose PE and a search for the source of thrombus in the inferior vena cava, deep pelvic venous system, cardiac cavities and the deep venous system of lower extremities.

A general toxicological analyses of blood and urine as well as histopathological study of all organs were carried out in the National Institute of Toxicology and Forensic Sciences, Seville. Sections of all organs were stained with H&E and Masson's Trichrome. Although pulmonary emboli and thrombi are macroscopically different from post-mortem clots, a microscopic study was carried out in all cases to confirm the diagnosis. In cases in which the origin of thrombus was found in the deep veins of lower extremities, samples of the veins with thrombus were studied histologically.

According to the level of the pulmonary artery vasculature involvement, the PE was classified as: (1) massive PE when the thrombus lodges in the main trunk of the pulmonary artery and extends to both branches, (2) PE affecting the proximal right or left pulmonary arteries and (3) PE affecting the segmentary branches.¹⁴

In addition to the post-mortem findings, the following clinical-epidemiological variables were recorded: Age and sex, place of death, time of death (divided into three time groups: 0–8 a.m., 8 a.m.–4 p.m. and 4–12 p.m.) and season in which the death took place; pathological history and risk factors for thromboembolism: Diabetes mellitus, systemic hypertension, immobilization, previous surgery, previous trauma, tumors and cardiovascular pathology; medication taken in the last two months; symptoms prior to death and the period of time elapsed between the beginning of symptoms and death; anthropometric measurements such as the body mass index (BMI) and the waist circumference (WC). To define obesity, according to the BMI, we followed the Word Health Organization criteria¹⁷ (overweight 25–29.9 kg/m² and obesity >30 kg/m²). Central or visceral obesity, according to WC, was defined if ≥94 cm for men and ≥80 cm for women. However, central obesity was considered of high cardiovascular risk if >102 cm in men and >88 cm in women.¹⁸

Descriptive statistical analysis of the data was performed using SPSS for Windows version 15.0.

3. Results

Incidence of PE as cause of sudden death: In the study period 2477 forensic autopsies were performed, with 55% (1363) corresponding to violent deaths (homicides, suicides or accidents) and 45% (1114) to natural deaths. Six hundred and sixty-eight of the natural deaths (668/1114 = 60%) fulfilled the criteria of sudden death. There were 32 cases of death by PE, from which three cases were linked back to an initiating accidental injury and from a medico-legal point of view they were considered accidental deaths. The remaining 29 cases of PE were sudden natural deaths, which represents 4.3% of sudden deaths, 2.6% of natural deaths and 1.2% of total deaths.

Distribution by age and sex: 19 cases (59.4%) were men and 13 cases (40.6%) were women. This represents a male–female ratio of 1.5:1. The global average age was 53.8 ± 18.4 years (58.9 ± 23.3 years for women and 50.3 ± 13.8 years for men; $p = NS$) ranging from 18 to 87 years for women and 22 to 74 years for men. There was no case under 18 years of age, but 12 cases (37%) were younger than 45 years (7 men and 5 women). The distribution of cases according to age and sex is represented in Fig. 1.

Level of pulmonary vasculature involvement, source of thrombus and presence of associated pulmonary infarction: 23 cases (72%) were massive PE, 3 cases (9%) had thrombi occluding the proximal left pulmonary artery and in six cases (19%) the presence of thrombotic material was observed occluding segmentary branches in both lungs. In 22 cases (69%) the thrombus originated in the deep venous system of lower limbs and in 1 case (3%) the origin was a mural thrombus lodged in the right ventricle (48 years old male with antecedents of chronic alcoholism who died suddenly at home). From these 22 cases, in 13 the origin was the right calf, in 8 the left calf, 1 in the right thigh. In 9 cases (28%), the origin of the thrombus was not identified. Microscopic examination of them showed well organized thrombi composed by platelets and erythrocytes into a matrix of fibrin. In the histological sections of the deep leg veins studied, we did not observe inflammatory changes in the walls indicative of thrombophlebitis. Pathological study showed pulmonary infarction in only 2 cases (6%), (cases 6 and 5 in Tables 2 and 3, respectively), characterized by coagulative necrosis of the lung substance within an area of hemorrhage and edema with small vessels occluded by organized thrombi.

Place of Death: In 26 cases (81%) death occurred at home or during the transfer to a health care centre. In two cases (7%) patients were hospitalized in a Psychiatry Unit. In the remaining four cases (12%), death occurred in a public place, including a case during a train trip.

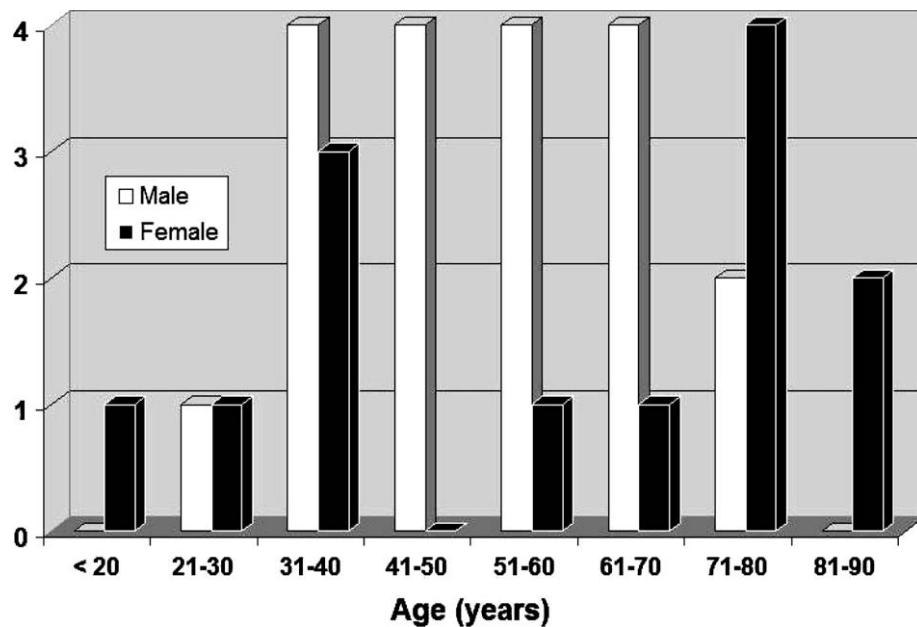


Fig. 1. Distribution of PE cases according to age and gender.

Time of death: 22 deaths (69%) occurred in the fall or winter. The 10 remaining cases (31%) occurred in the spring or summer. In relation to the time of death, in 15 cases (47%) death occurred between 8 a.m. and 4 p.m., in nine cases (28%) between 0 and 8 a.m. and in 8 cases (25%) between 4 p.m. and 12 p.m.

Pathological antecedents and risk factors for PE: There were antecedents of surgery in seven cases (21.9%). In nine cases (28.1%) patients were immobilized in relation to previous surgery or with organic and/or psychiatric pathology. With respect to obesity, the average BMI was $31.5 \pm 8.1 \text{ kg/m}^2$ (29.8 ± 8.4 for men and 34.2 ± 7.2 for women). In 24 cases (75.0%) the BMI was greater than 25 kg/m^2 , with overweight existing in seven cases (21.9%) and obesity in 17 cases (53.1%). The average AP was $100.4 \pm 17.8 \text{ cm}$ ($99.5 \pm 21.3 \text{ cm}$ for men and $101.6 \pm 11.5 \text{ cm}$ for women). The WC was considered to be of high cardiovascular risk in 36.9% of the men and 69.2% of the women. The other pathological antecedents and known risk factors for PE in this series are represented in Table 1. None of the women was pregnant, taking oral contraceptives or hormone replacement therapy.

Chronic therapy: 10 cases (31%) had habitual prescription for systemic hypertension (four cases), diabetes mellitus (three cases)

and chronic heart failure (three cases). A history of psychiatric pathology existed in 10 cases (31%) and six of them (19%) had psychotropic treatment as represented in Table 2. In only three cases (9%) thromboembolic prophylaxis was prescribed.

Symptoms prior to death: 10 cases (31%) presented dyspnea, six cases (19%) chest pain and three cases (9%) syncope. In addition, 10 cases (31%), complained of pain in the lower limbs on the days prior to death. In six cases (19%) patients went to an Emergencies Department (out-of-hospital or hospital) due to symptoms compatible with DVT/PE but this diagnosis was not suspected in any case and therefore, no therapeutic measures were adopted. The characteristics of these patients are described in Table 3.

4. Discussion

In this study, PE was the main cause of death in 1.2% of the total forensic autopsies. This percentage is within the previously reported range of 0.8%, obtained at the Office of the Chief Medical Examiner of New York⁸, and 2.5% referred to by the Department of Legal Medicine of the University of Kitasato.¹⁹ Studies carried out on series of hospital autopsies indicate a greater percentage of PE (between 3.9% and 5.8%)^{13,14,20} than that obtained in forensic autopsies. This difference is logical since hospital autopsies are performed on admitted patients who have more risk factors for the development of PE than the general population on which the forensic autopsies are performed.

In our series, the maximum seasonal incidence was obtained for the fall and winter (69%), which is in agreement with the majority of published studies^{21–24} although this seasonal predominance was not found in others.^{25,26,7,13} This fact is explained by the influence of cold weather on vasoconstriction and the fibrinolytic system, along with a diminution in physical activity.²²

The source of PE was identified in 72% of cases; most of them (96%) were localized in the deep venous system of the lower limbs, mainly in calves, and in only one case (4%) in a thrombus lodged in the right ventricle. Most patients with PE have an associated DVT which usually starts in the calf veins from where it may extend to the proximal veins.²⁷ The aggregate incidence obtained from several studies of lower limb thrombosis in unselected autopsies was 43% being the incidence of thrombi in the calves (44%) higher

Table 1
Pathological antecedents and risk factors for PE

Pathological antecedents and risk factors for PE	Number of cases	Observations
Overweight and obesity	24	Overweight: 7; obesity: 17
Immobilization	9	One case of Steinert muscular dystrophy
Hypertension	7	4 with pharmacologic treatment
Diabetes mellitus type II	5	3 with pharmacologic treatment
Chronic heart failure	3	3 with pharmacologic treatment
Orthopedic/trauma surgery	4	Meniscectomy by arthroscopy hallux valgus operation, hip fracture, arm fracture
Other surgery	3	Subdural hematoma, oligodendrogloma, craniopharyngioma
Peripheral circulatory insufficiency	3	Thromboangiitis obliterans, chronic venous insufficiency (2)
Previous PE	1	21 years before
Tumors	3	Colon cancer, oligodendrogloma, craniopharyngioma

Table 2

Data from 10 patients with PE and history of psychiatric disorders

Case	Age and sex	Psychiatric diagnosis	Prescribed treatment	Place of death	Toxicological analysis (blood)
1	18, F	Infantile psychosis	Risperidone, clorazepate, biperiden, clorazepate	DOA in hospital	Levopromazine: 0.03 mg/l nordazepam: 0.15 mg/l
2	38, M	Schizophrenia, epilepsy	None	Home	Ethanol: 0.12 g/l
3	41, M	Schizophrenia, mental retardation	Carbamazepine, clorazepate, topiramate	Nursing home	Carbamazepine: 0.82 mg/l topiramate: 5.49 mg/l nordazepam: 0.73 mg/l oxazepam: 0.21 mg/l
4	42, M	Psychosis not specified, alcoholism	None	Home	Ethanol: (<0.1 g/l) Δ9 thc: 49.3 ng/ml
5	53, M	Schizophrenia, mental retardation	Risperidone, lorazepam, gabapentin, paroxetine	Psychiatric unit	Biperiden: 1.66 mg/l
6	60, F	Bipolar disorder	Olanzapine, clorazepate, carbamazepine, clorazepate, lorazepam	Psychiatric unit	Carbamazepine: 4.18 mg/l nordazepam: 1.33 mg/l
7	67, M	Depression	None	DOA in health centre	Metabolite of pentoxifylline (vasodilator)
8	79, F	Depression	Thioridazine, lorazepam, citalopram, maprotiline	DOA in hospital	Ethanol: 0.12 g/l
9	39, F	Depression	Imipramine, levopromazine	Home	Ethanol: 0.17 g/l imipramine: 1.20 mg/l levopromazine: 0.26 mg/l
10	38, F	Schizophrenia, mental retardation	None	Home	Ethanol: 0.56 g/l

DOA, dead on arrival; Δ9 THC, delta 9 tetrahydrocannabinol.

than in the thighs (17%) and thrombi in the thighs alone are the less common. This distribution of thrombi within the legs suggests that local factors are important and numerous anatomic structures have been cited as source of pressure causing decreased flow. Examples of these structures are the soleus muscle, which compresses the posterior tibial vein, the adductor ring, which compresses the popliteal vein, and the inguinal ligament, which compresses the femoral vein.²⁸

In a minority of cases (6%) the existence of associated pulmonary infarction was observed. This low percentage is not surprising if it is considered that only 10% of the total of PE (fatal and non-fatal) progress towards pulmonary infarction. This situation may be explained because of the dual blood flow into the area from the bronchial circulation. For that reason pulmonary infarction is very infrequent unless previous cardiac and/or respiratory diseases coexist, or a progressive release of thrombi occurs from the lower extremities to the small end-arteriolar pulmonary branches. In most cases of PE presenting as sudden death (as those of this series) an acute occlusion of the main pulmonary arteries takes place, without time to produce an infarction.²⁹

Much emphasis has been placed on the risk of PE in surgical patients but it is necessary to consider that in nearly 80% of recent series, PE develops in non-surgical patients.²⁰ These results are similar to those obtained in our series, in which only 22% of cases had a history of prior surgical treatment.

Some authors have tried to establish a greater risk of PE in psychotic disorders and the administration of neuroleptic drugs. In previous studies^{30,31}, 37–44% of patients diagnosed with PE were taking antipsychotic drugs, whereas others found that in 16% of deaths due to PE a psychotic disorder existed, mainly in women.¹⁹ For these reasons, some authors hypothesize that antipsychotic treatment represents an important risk factor for PE, especially in females. Although the cause of this high proportion of deaths by PE in patients with psychotic disorders is unknown, it is postulated that it may be related to a reduced mobility (hypokinetic state) along with a possible prothrombotic effect of neuroleptics.¹⁹ In our study, 10 cases (31%) presented psychiatric disorders and in 6 of them had prescribed treatment with neuroleptics. However, toxicological analysis showed the presence of levopromazine in only two cases. Our results indicate that psychiatric disorders appear in a considerable percentage of patients who developed PE, as to support the view that it should be considered as an additional risk factor for PE.

In studies from hospitalized patients and from the general population it has been considered that obesity is a risk factor for DVT and PE, especially in women.^{32,33} In our series 75% of cases were overweight (22%) or obese (53%), percentages much greater than those observed for the Spanish Society for the Study of Obesity (SEEDO) in the year 2000. The prevalence of obesity in this study was 14.5% (13.4% in men and 15.8% in women).³⁴ In terms of WC, more than a third of men (37%) and more than two-third of women (69%) in our series, presented a WC considered to be of high cardiovascular risk.¹⁸ It is known that abdominal obesity is associated to a greater incidence of diabetes, systemic hypertension, dyslipidemia, cardiovascular disease, prothrombotic processes as well as sedentarism.³⁵ In summary, our data are concordant with those of previous studies with respect to the high proportion of obesity among patients with PE. Nevertheless, controversy exists with respect to whether obesity constitutes an independent risk factor for PE, as it is supported by some studies³⁶, but not others.³⁷

Apart from the exposed and common acquired risk factors for thromboembolic events, there are some inherited thrombophilic disorders (hereditary thrombophilias) which may play an important role in the predisposition to form clots. This hereditary thrombophilias include factor V Leiden leading to activated protein C resistance (APCR), prothrombin gene mutation, and deficiencies

Table 3

Data from six cases with PE previously examined in an emergency service

Case	Age/Sex	Motive of Consultation	Diagnosis	Treatment
1	61, M	Right leg pain	Muscular rupture	Non steroid anti-inflammatory drugs
2	82, F	Dyspnea and right leg pain	Osteoarthritis	Non steroid anti-inflammatory drugs
3	55, M	Dyspnea and chest pain	Respiratory Insufficiency without evidence of pneumonia	Antibiotics, mucolytics and bronchodilators
4	28, F	Right leg pain (examined in emergencies service at health centre and hospital)	Mechanical pain	Not recorded
5	50, M	Left leg pain lasted 2 months (off work)	Sciatica	Repose and non steroid anti-inflammatory drugs
6	39, M	Right leg pain lasted 1 month	Hyperuricemia	Not recorded

of antithrombin (I, II and III), protein C or protein S. APCR (factor V Leiden) is the most common inherited defect of the coagulation known to date and is found in 21% of individuals with DVT⁹ but may be a milder genetic risk factor for PE.³⁸ Studies carried out in medical examiner centres have found that the prevalence of APCR in people who die suddenly of PE is similar to the general American or Finnish population implying that most fatal PE seen in forensic setting are not induced by APCR.^{9,10} The consequence is that routine post-mortem testing for this genetic disorder is not indicated and should be only considered if there is a recurrent venous thrombosis or a family history of venous thrombosis, and if thrombosis presents in adolescence.⁹ Other authors agree with this opinion considering that these tests are expensive and should be reserved for selected cases.^{7,8} From a clinical point of view some studies suggest that prothrombotic abnormalities do not appear to play an important role in the risk of a recurrent thrombotic event. Testing for prothrombotic defects has little consequence with respect to prophylactic strategies and clinical factors are probably more important than laboratory tests in determining the duration of anticoagulant therapy.³⁹

The concurrence of typical symptoms and signs (dyspnea, chest pain and hemoptysis) occurs in less than 25% of cases.⁴⁰ In our study, the most frequent symptoms prior to death were: dyspnea (31%), chest pain (19%) and syncope (9%). A third of the cases (31%) complained of pain in the lower limbs on the day prior to the death and 6 of them (19%) asked for medical attention in an emergencies department for symptoms compatible with DVT/PE, but this diagnosis was not suspected, nor was the suitable treatment applied. The absence of clinical suspicion of PE in emergency services oscillates between 25% and 70% according to different studies.^{41,42} Autopsy studies demonstrate that an embolus often develops without clinical symptoms or with very unspecific symptoms.^{20,27,41} The scarce specificity of the symptoms and the fact that PE can affect both healthy and unhealthy subjects, make its clinical suspicion difficult. These errors of diagnosis frequently lead to the presentation of complaints of professional negligence as happened in two cases in our series.

An inherent limitation to the nature of this study is that it analyzes the incidence of fatal cases of PE in a series of judicial autopsies; therefore, any extrapolation of these results to the general population must take into account the forensic setting of this study. Another limitation is that testing for hereditary thrombophilias was not performed. These tests might have added some additional information in a few cases, but the main results of this study would not have been affected.

In summary, PE is an entity with high mortality that frequently makes its debut as a sudden death, as is made clear in our study. In addition to the classic risk factors presented in most of the cases, this series emphasizes the very high prevalence of overweight/obesity (75%) as well as the high percentage of cases with a psychiatric antecedents and/or treatment (31%) which is why we consider that this association should be considered as a risk factor for PE. PE continues to be an important clinical problem which requires a high level of diagnostic suspicion. In the days prior to death 19% of our cases sought medical attention for symptoms compatible with PE. However, in none of them was the correct diagnosis reached. In these cases, the possibility of avoiding the fatal outcome would have existed if PE was considered as one of the different diagnostic options and adequate therapeutic measures would have been adopted.

Conflict of interest statement

None.

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Ethical approval

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